PRIMARY BILIARY CHOLANGITIS (PBC)

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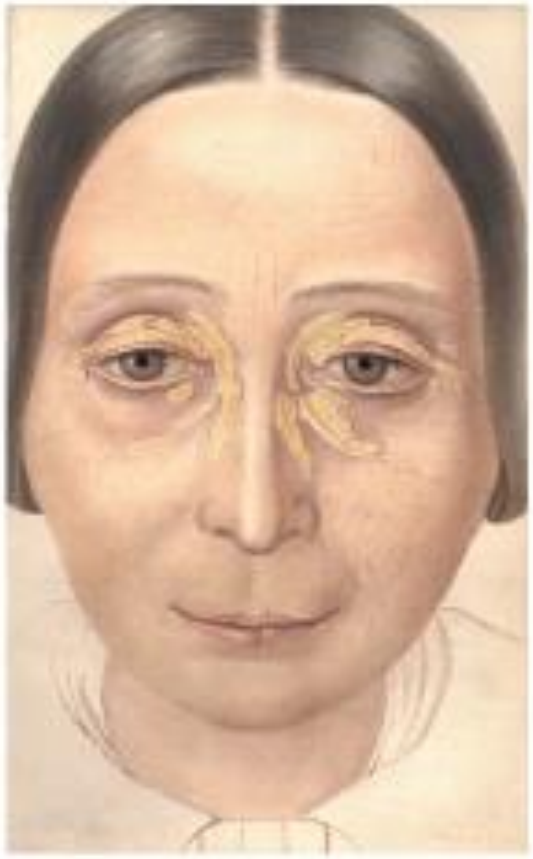
Objectives

- Inform and update on management of PBC
- To understand the current therapy and their limitations;
- To recognise the importance of pruritus (itch) PBC
- To update current research and future directions.

The Human Face of Primary Biliary Cholangitis

Chronic Cholestasis



Addison & Gull *Guys Hospital Review 1857*

Features of End Stage Disease

Death

Jaundice
Coagulopathy
Encephalopathy
Ascites
Varices

Features Seen at all Stages

Reduced Quality of Life

Fatigue
Cognitive impairment
Pruritus

Asymptomatic Disease

Newcastle University

UK-PBC

Illustrative case

- 32 yr F
- Presents to her GP with vague abdominal pain and tiredness;

- Liver biochemistry:
  - Bilirubin 10 (µMol/L)
  - ALT 30 IU/L,
  - AST 22 IU/L,
  - ALP 325 IU/L,
  - Albumin 41 g/L

- US abdomen: Normal liver and biliary system

What are the causes of raised ALP?

- Puberty related bone growth
- Pregnancy

- Biliary obstruction
- Gallstones
- Drug induced cholestasis
- Primary biliary cholangitis

- Vitamin D deficiency
- Paget's disease
- Non alcohol fatty liver disease

Suspected PBC- What test?

- Cholestatic LFTs (ALP >ALT or AST)
- US abd: Normal biliary system→ no extrahepatic obstruction
- Liver auto antibodies:

➢Anti-mitochondrial antibody: Positive, M2 positive, 1:640

➢Anti- nuclear antibody: Weakly positive

➢Anti-smooth muscle antibody: Negative

➢Anti-LKM antibody: Negative

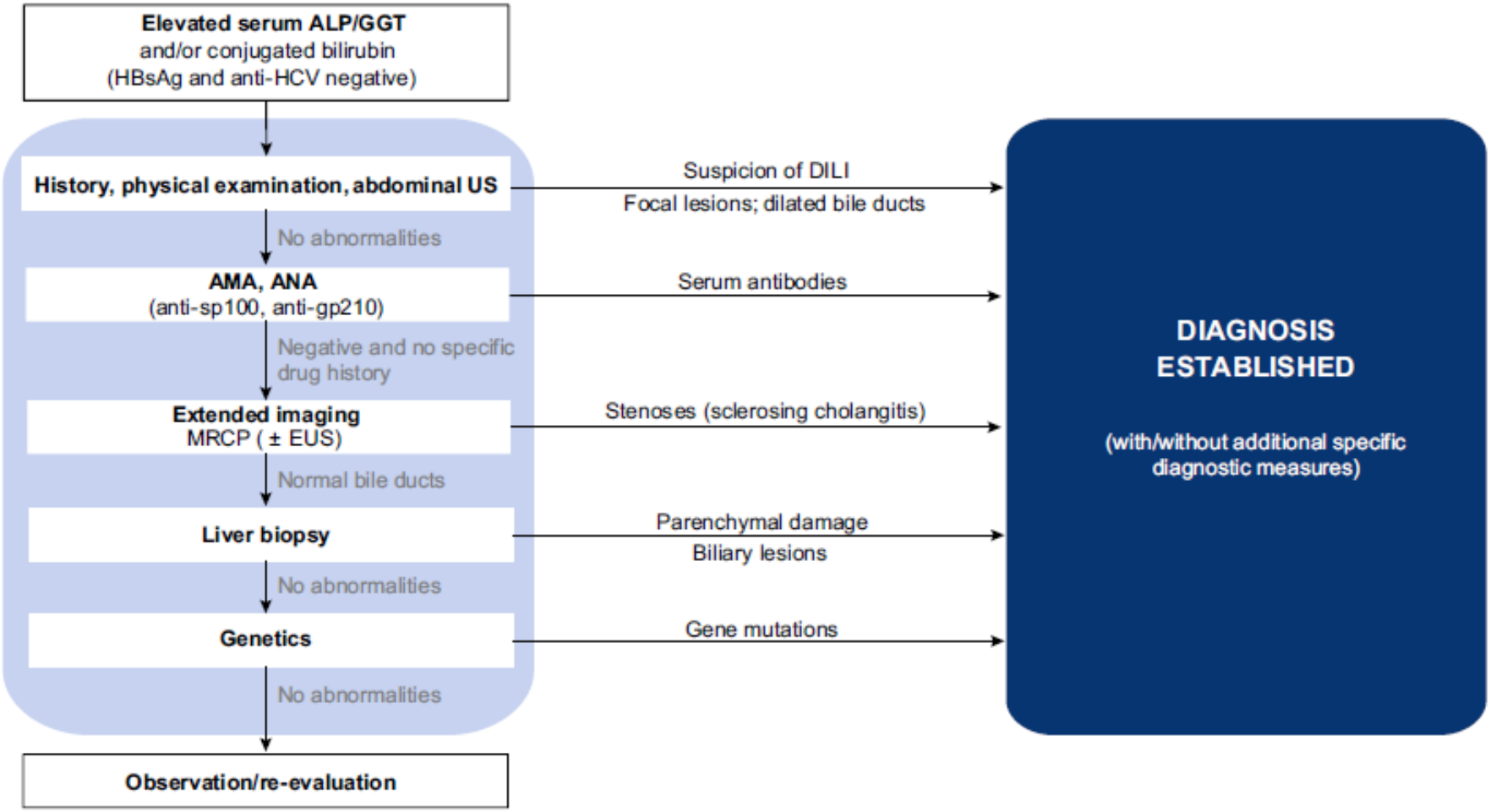
➢Immunoglobulins: IgG 10; IgM 6.2, IgA 2.0

Utility of investigations in PBC

Test	Finding	Suspicion	Diagnosis	Prognosis
ALP	↑	✓	✓	✓
AST/ALT	↑	✓		✓
GGT	↑	✓		
IgM	↑	✓		
AMA (>1/40)	+		✓	
Specific ANA	+		✓	
anti-gp210	+		✓	✓
anti-sp100	+		✓	
anti-centromere	+			✓
Bilirubin	↑			✓
Platelets	↓			✓
INR	↑			✓
Albumin	↓			✓

EASL Guidelines 2017

Diagnosis of PBC

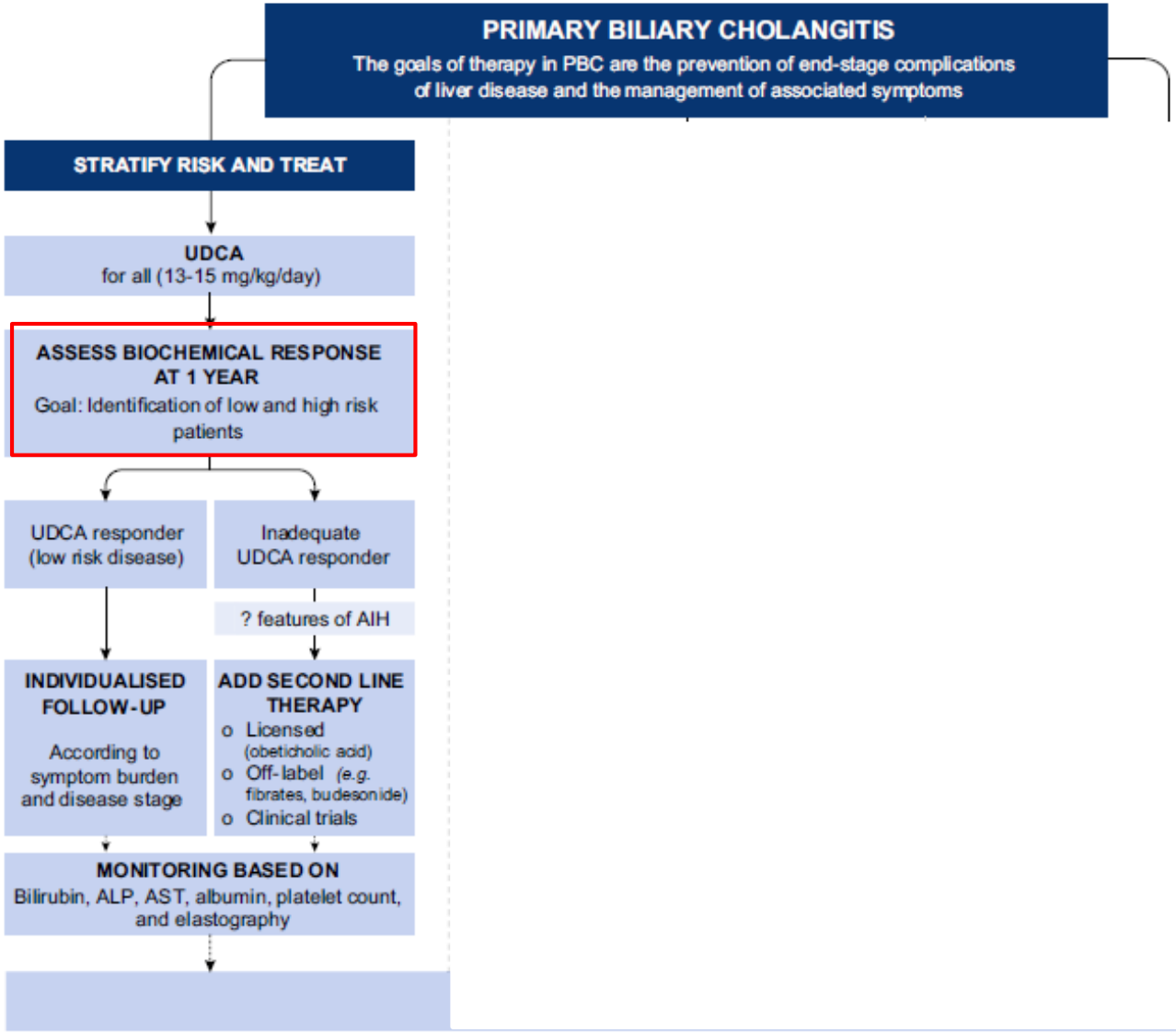


EASL Guidelines 2017

Case (contd)

- Diagnosis of PBC made
- What next?
- Start Ursodeoxycholic acid (UDCA, Urso)
- *Dose: 13-15mg/Kg/day*
- Indefinite, lifelong treatment

Medical Management of PBC



What is UDCA (Urso) response?

Criteria	Assessment time	Biochemical response
Rochester (24)	6 months	AP < 2 x ULN and Mayo score < 4.5
Barcelona (25)	1 year	AP decrease > 40% or normal levels
París I (26)	1 year	AP ≤ 3 x ULN, AST ≤ 2 x ULN, Br < 1 mg/dL
París II (27)	1 year	AP ≤ 1.5 x ULN, AST ≤ 1.5 x ULN, Br < 1 mg/dL
Róterdam (28)	1 year	Br and albumin, normal
Toronto (29)	2 years	AP < 1.67 x ULN
Mayo (30)	1 year	AP < 2 x ULN

ULN: upper limit of normal; Br: bilirubin; AP: alkaline phosphatase.

Case (contd)

- Started on UDCA 1000mg OD

- After 1 year:

➢ ALP 270

➢ AST 28

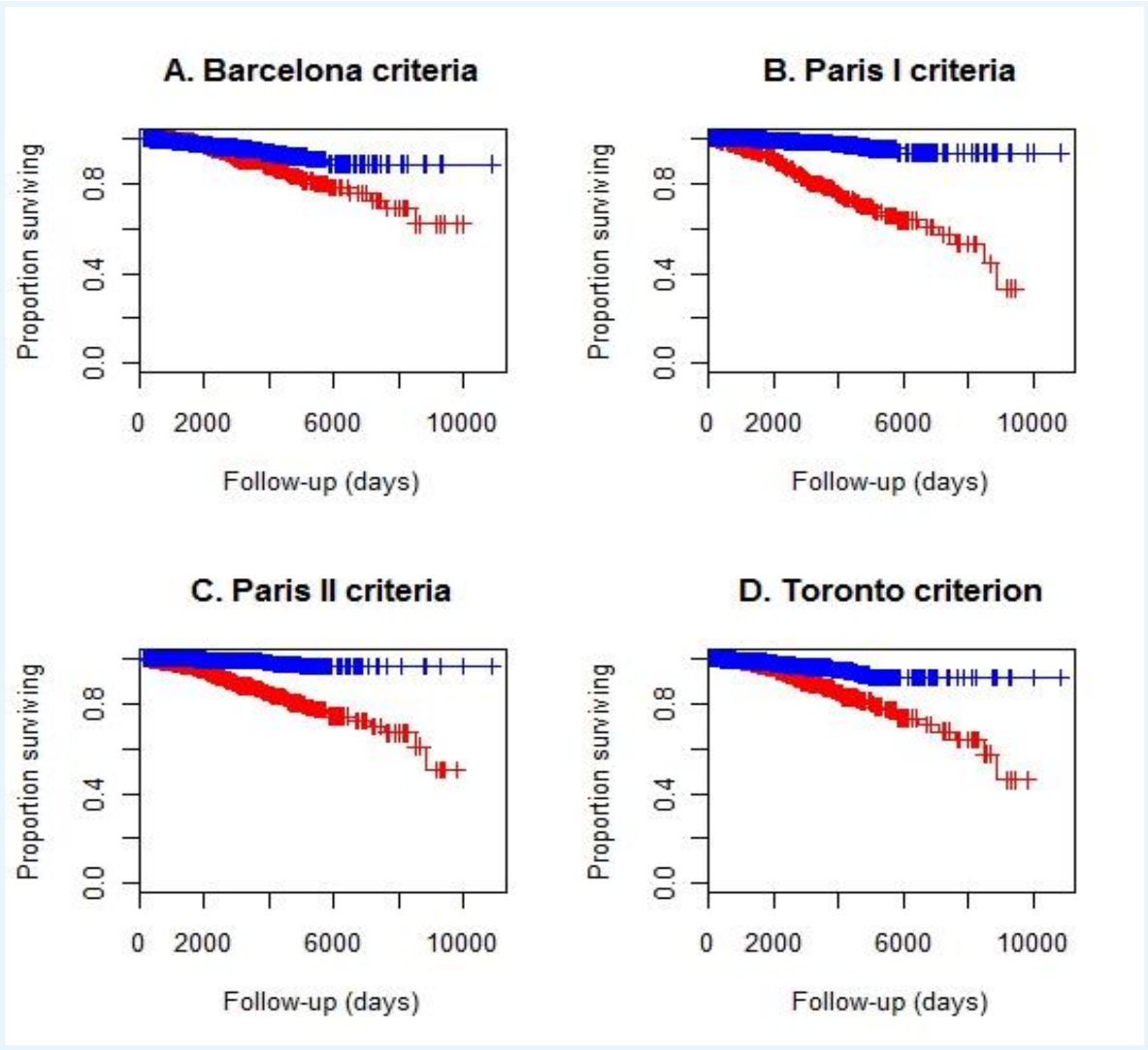
➢ ALT 31

➢ Bilirubin 22

➢ Albumin 39

➢ *Is she UDCA responder? Or non-responder?*

UDCA Response/Non-Response determines Risk



Carbone et al **Gastroenterology** 2013

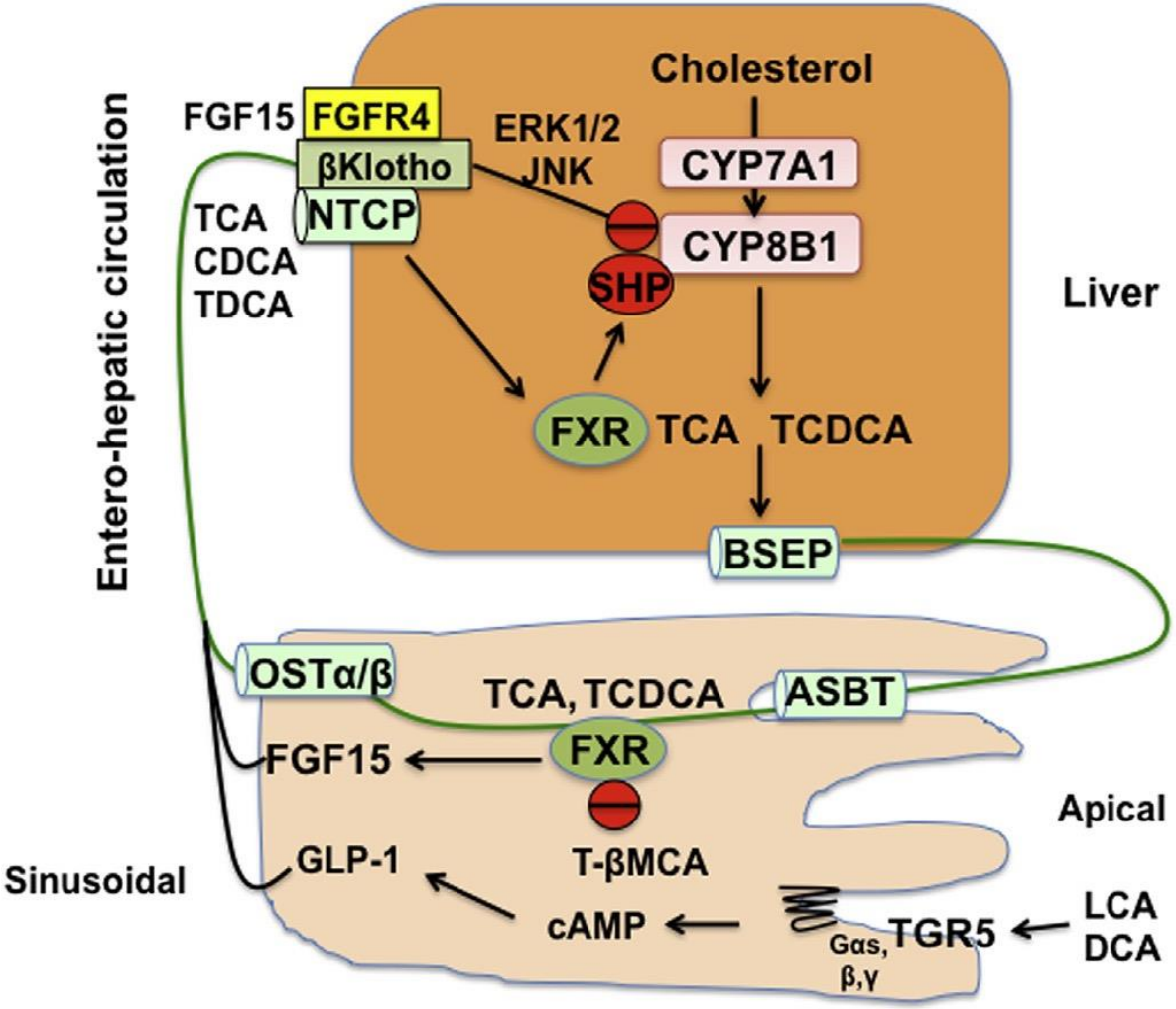
Treatment of UDCA non-responder

- *Do not stop UDCA*
- Consider 2nd line treatments

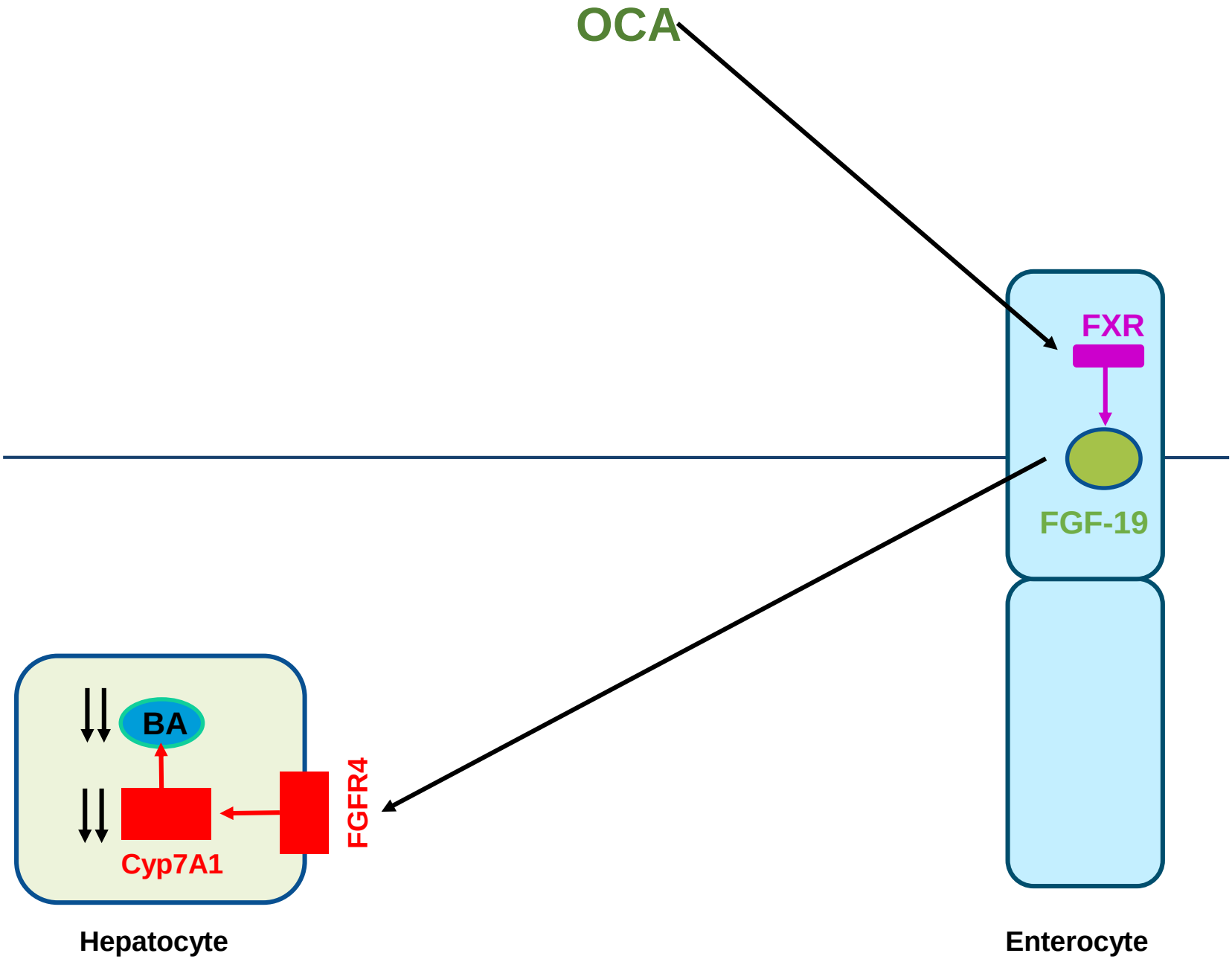
➢ Obeticholic acid (Ocaliva™, Intercept)

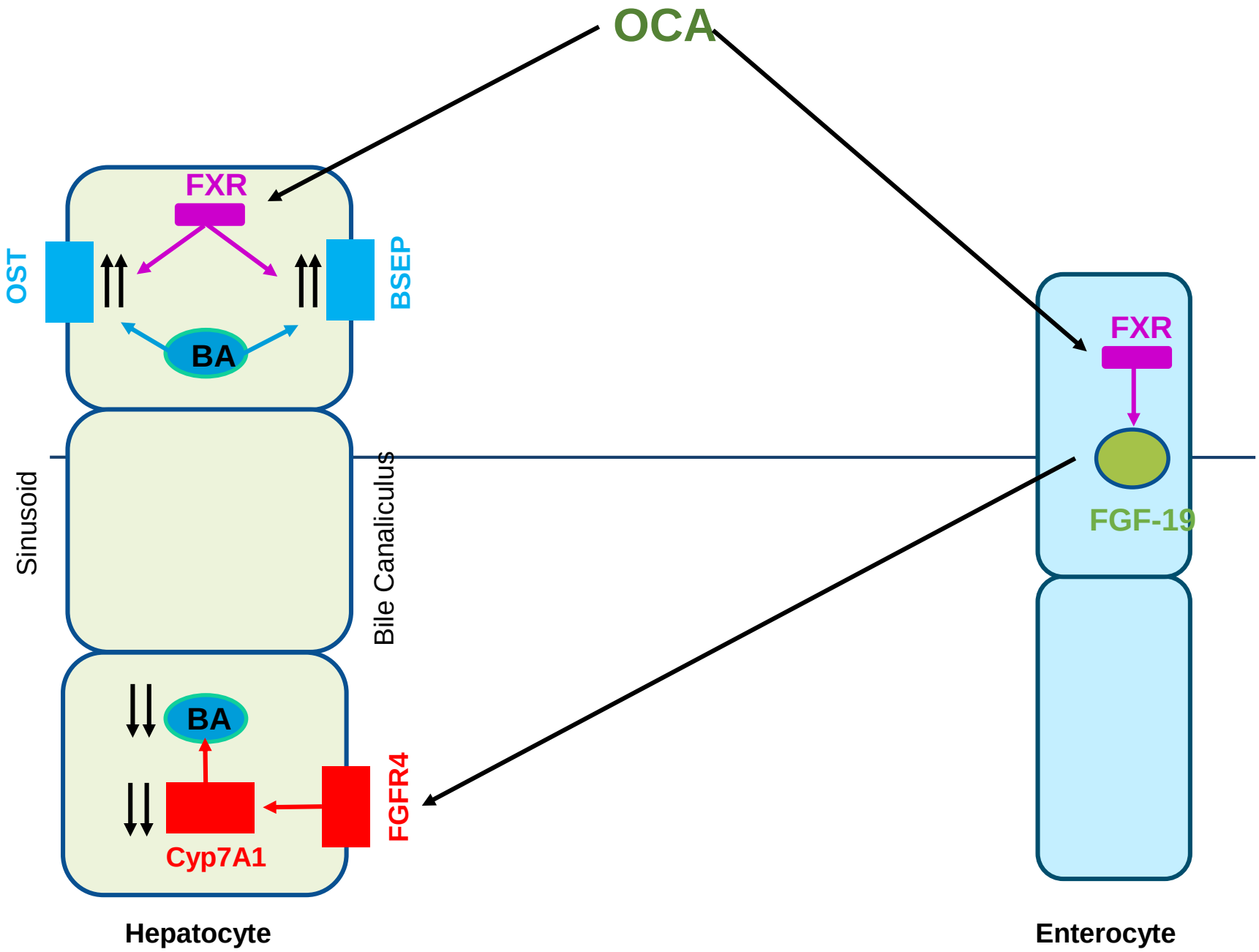
➢ Fibrates (off licence; Bezafibrate, Fenofibrate)

Obeticholic acid: FXR agonist



Chiang, Live Research 2017


OCA
FXR
FGF-19
BA
Cyp7A1
FGFR4
Hepatocyte
Enterocyte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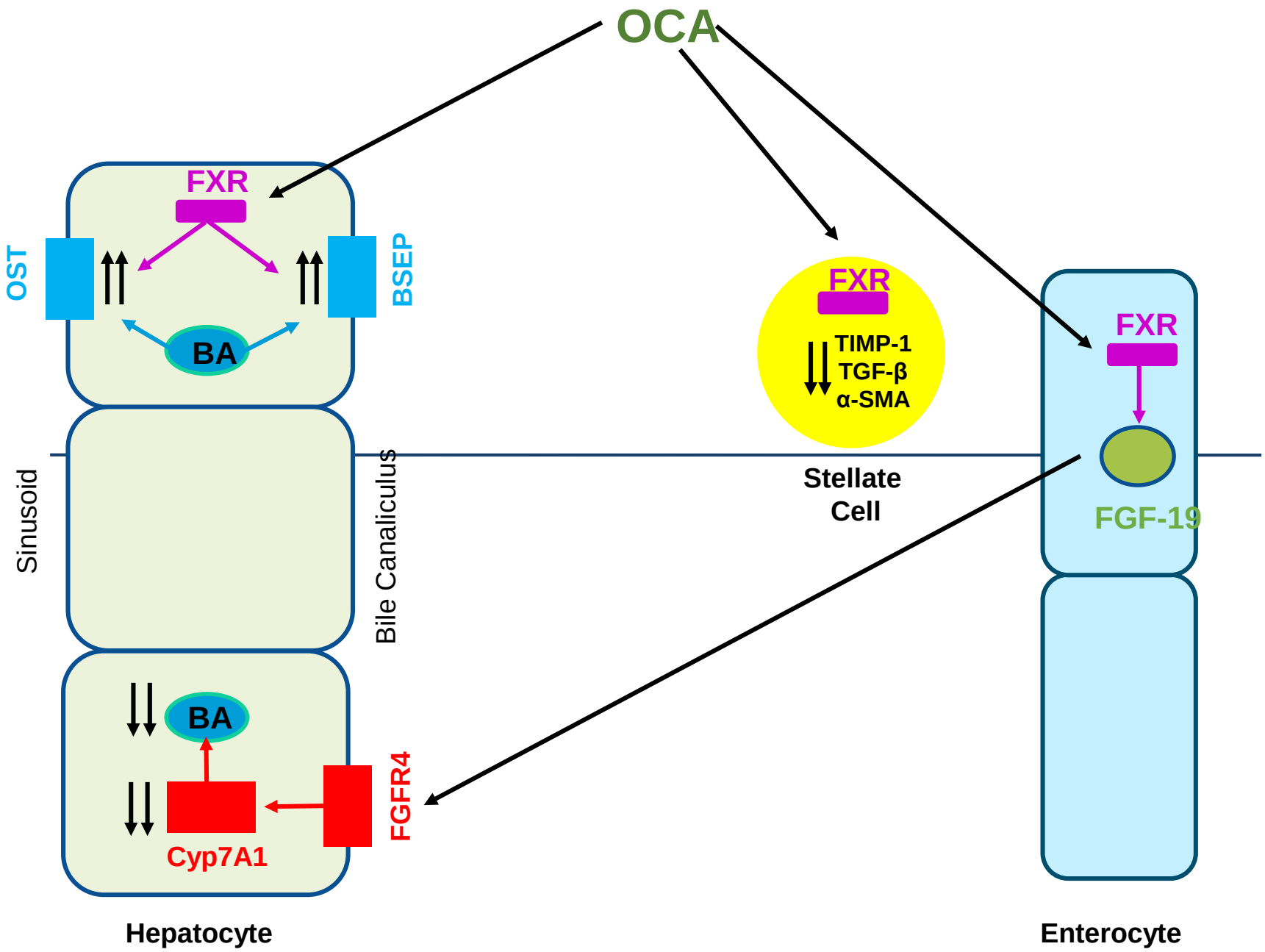
Sinusoid
Bile Canaliculus
FXR
FGF-19
BA
FGFR4
Cyp7A1
Hepatocyte
Enterocyte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TGF-β
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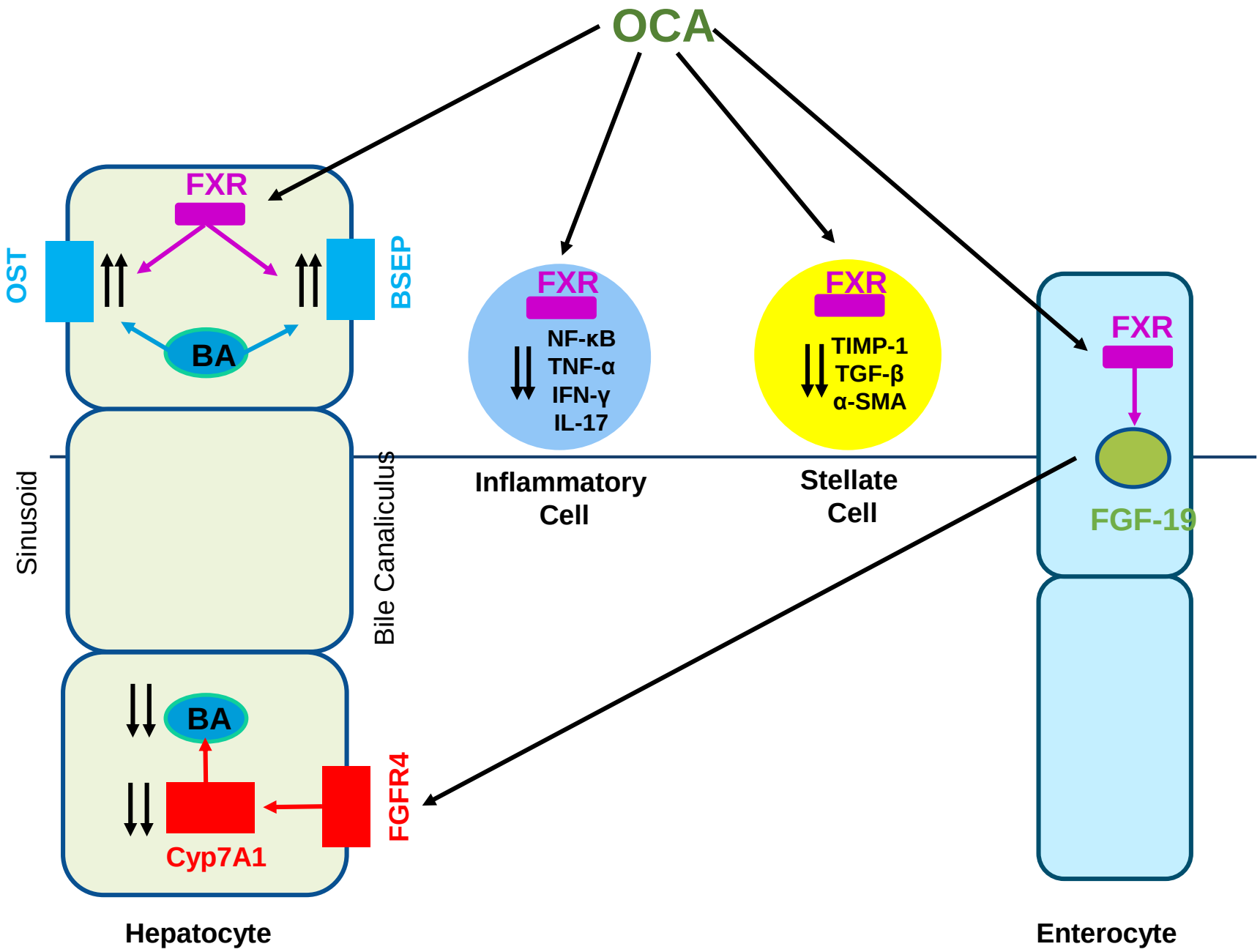
Bile Canaliculus
Stellate
Cell
BA
FGFR4
Cyp7A1
Hepatocyte
Enterocyte


OCA
FXR
OST
BSEP
BA
Sinusoid
Bile Canaliculus
FXR
NF-κB
TNF-α
IFN-γ
IL-17
Inflammatory Cell
FXR
TIMP-1
TGF-β
α-SMA
Stellate Cell
FXR
FGF-19
BA
FGFR4
Cyp7A1
Hepatocyte
Enterocyte

Evidence for Obeticholic acid in PBC

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

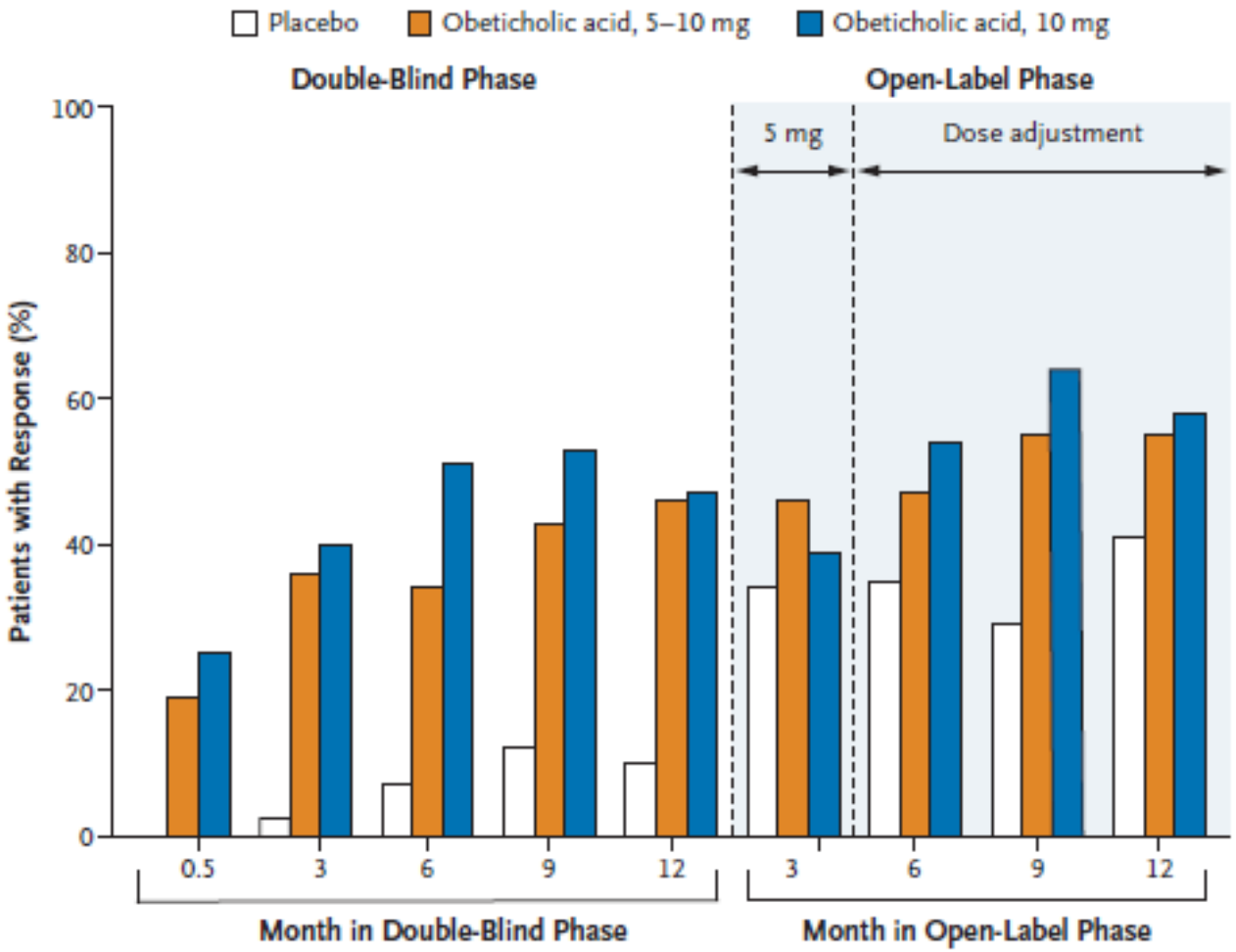
A Placebo-Controlled Trial of Obeticholic Acid in Primary Biliary Cholangitis

F. Nevens, P. Andreone, G. Mazzella, S.I. Strasser, C. Bowlus, P. Invernizzi, J.P.H. Drenth, P.J. Pockros, J. Regula, U. Beuers, M. Trauner, D.E. Jones, A. Floreani, S. Hohenester, V. Luketic, M. Shiffman, K.J. van Erpecum, V. Vargas, C. Vincent, G.M. Hirschfield, H. Shah, B. Hansen, K.D. Lindor, H.-U. Marschall, K.V. Kowdley, R. Hooshmand-Rad, T. Marmon, S. Sheeron, R. Pencek, L. MacConell, M. Pruzanski, and D. Shapiro, for the POISE Study Group*

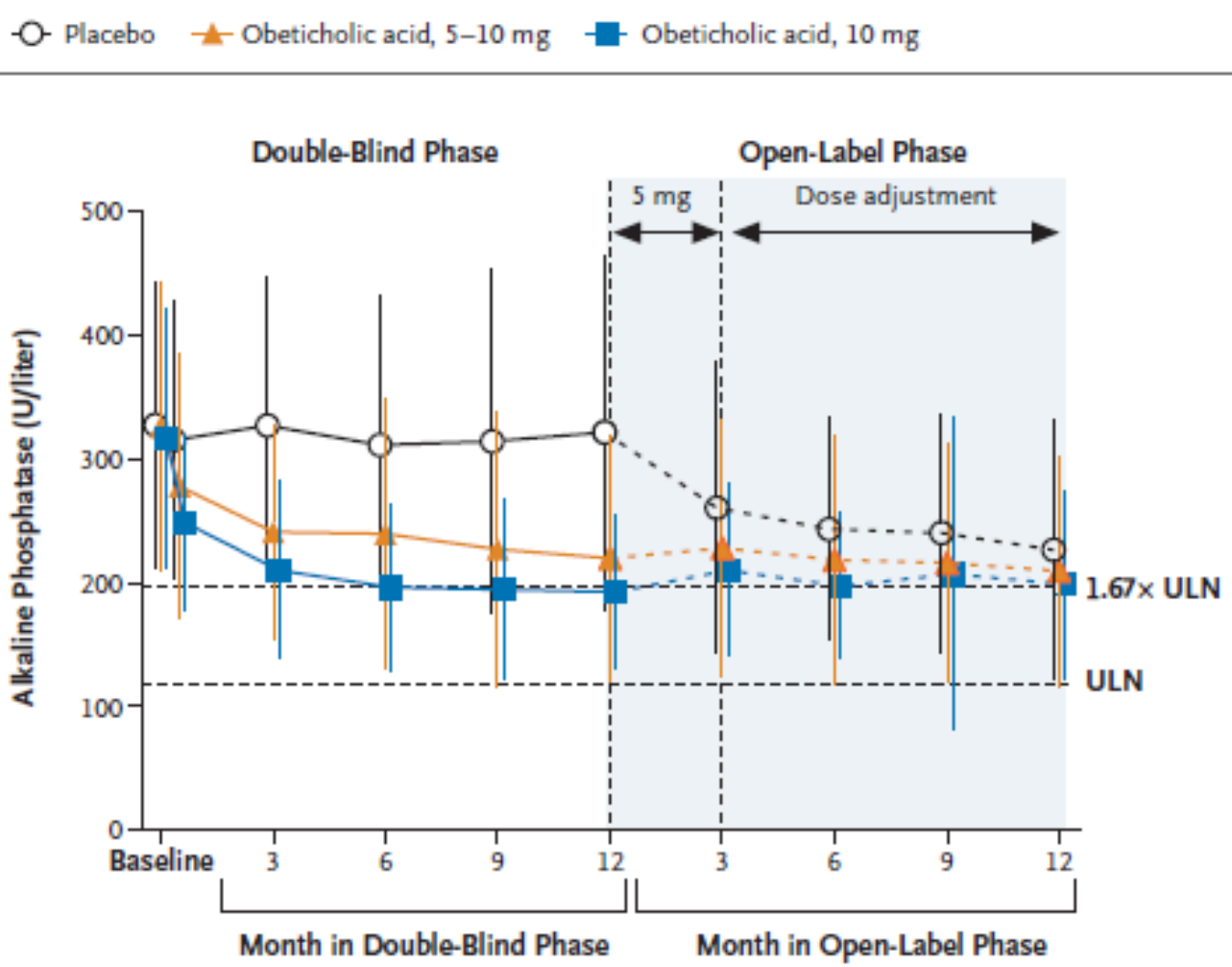
NEJM Aug 2016

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Placebo (N=73)	Obeticholic Acid, 5–10 mg (N=70)	Obeticholic Acid, 10 mg (N=73)
Age — yr	56±10	56±11	56±11
Female sex — no. (%)	68 (93)	65 (93)	63 (86)
White race — no. (%)†	66 (90)	67 (96)	70 (96)
Alkaline phosphatase			
Mean value — U/liter	327±115	326±116	316±104
≥1.67× ULN — no. (%)	72 (99)	69 (99)	73 (100)
Total bilirubin			
Mean value — mg/dl‡	0.69±0.42	0.60±0.33	0.66±0.39
>ULN — no. (%)	7 (10)	4 (6)	7 (10)
Ursodiol			
Use at baseline — no. (%)	68 (93)	65 (93)	67 (92)
Daily dose — mg/kg	15±4	17±5	16±5
Age at diagnosis — yr	47±9	48±12	47±11
Duration of disease — yr	8±5	8±6	9±7
Pruritus — no. (%)	47 (64)	37 (53)	44 (60)
Mayo Risk Score§	4.3±1.1	4.3±1.2	4.3±1.2
Liver stiffness¶			
Mean value — kPa	12.7±10.7	10.7±8.6	11.4±8.2
≥16.9 kPa — no./total no. (%)	7/39 (18)	7/35 (20)	6/32 (19)



No. of Patients									
Placebo	73	73	73	73	73	64	60	59	59
Obeticholic acid, 5–10 mg	70	70	70	70	70	63	62	62	60
Obeticholic acid, 10 mg	73	73	73	73	73	64	59	61	59



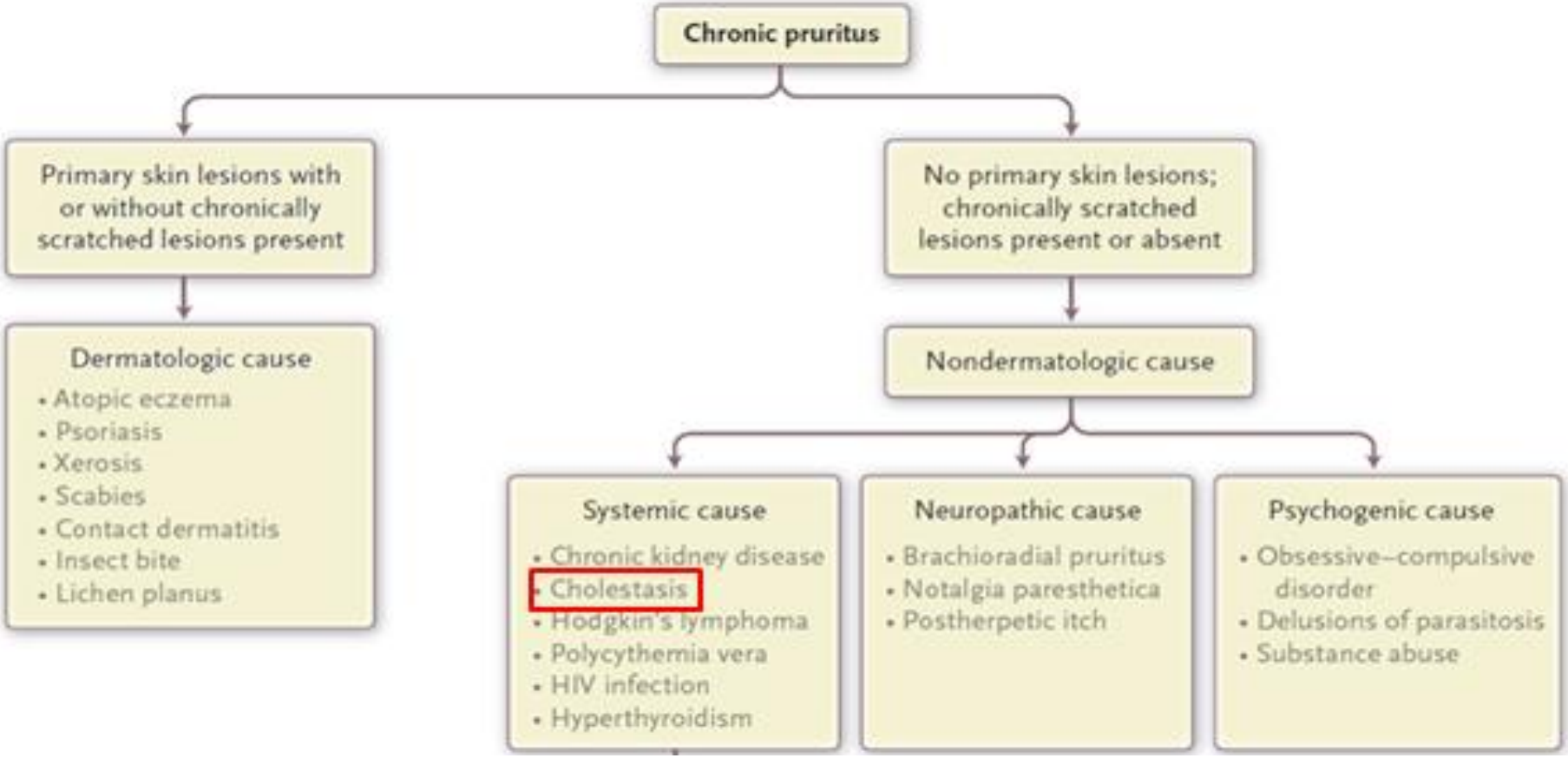
No. of Patients

Placebo	73	69	71	69	70	64	60	59	59
Obeticholic acid, 5–10 mg	70	69	69	66	64	63	62	62	60
Obeticholic acid, 10 mg	73	66	64	64	62	64	59	61	59

Pruritus (itch) in PBC

Causes of pruritus (itch)

- Irritating and unpleasant sensation that provokes the desire to scratch



Yosipovitch and Bernhard, NEJM 2013

Illustrative Case

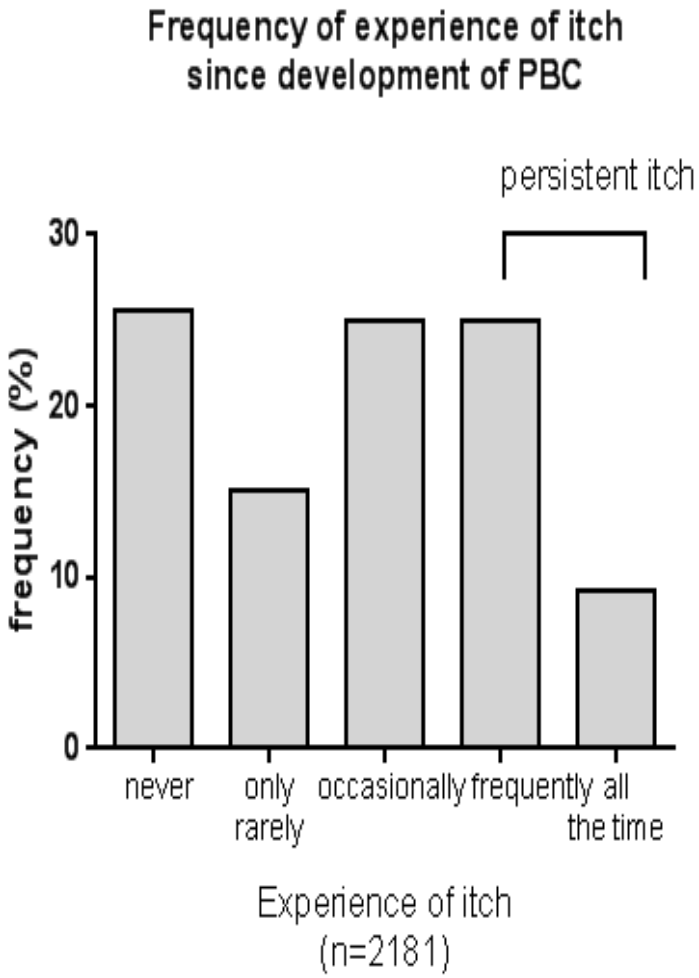
- 35 Yr, F, diagnosed of PBC ~3 years ago
- AMA+ve, M2+ve,
- Serum ALP 325 IU/ml
- Started on UDCA 1000 mg/day →ALP 270 IU/ml
- Itch since 9 months, intermittent, initially on forearms,
- Generalised itch, affecting night time sleep, embarrassment
- GP treating with Fexofenadine and Piriton; no response
- o/e: No skin rash, scratch marks in forearms, legs, abdomen

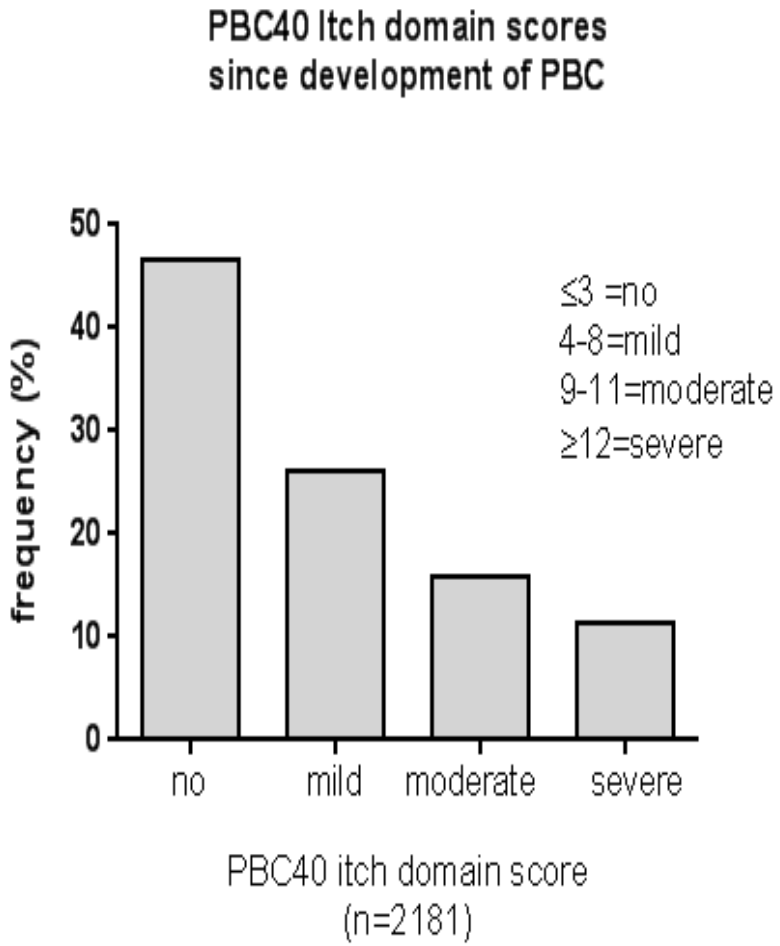
- How do we manage her pruritus?

I. Importance of pruritus in PBC

1. Itch is a common symptom and itch intensity is higher in younger patients.

Prevalence of pruritus in the UK-PBC cohort





Hegade *et al., Clinical Gastro &Hepatology* 2018

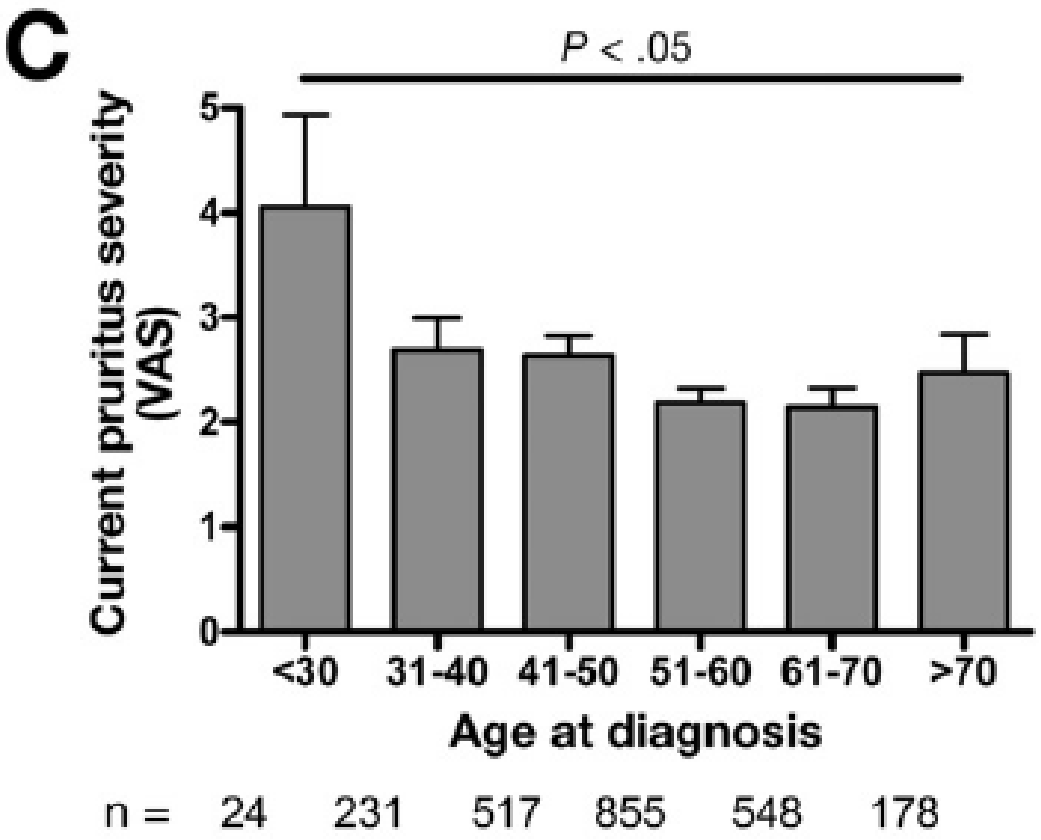
Initially asymptomatic patients likely to develop itch later

Table 3 Kaplan-Meier estimates of the proportion of initially asymptomatic patients developing symptoms of liver disease during the first 10 years of follow up

	Proportion of patients developing symptoms (%)		
	Time since diagnosis		
Symptoms	1 year	5 years	10 years
Itch	15.5	30.8	46.5
Fatigue	13.1	29.1	45.8
Hypochondrial pain	4.0	8.1	14.4
Bone pain	3.7	7.8	15.4
Ascites	1.7	8.1	16.7
Bleeding varices	1.0	3.4	9.2
Hepatic encephalopathy	1.3	3.7	8.7
Jaundice	2.8	9.0	17.0
Any symptom of PBC	26.4	50.7	71.3
Liver failure	3.0	12.2	23.6

Prince *et al* Gut 2004

Younger age at presentation =higher level of itch severity



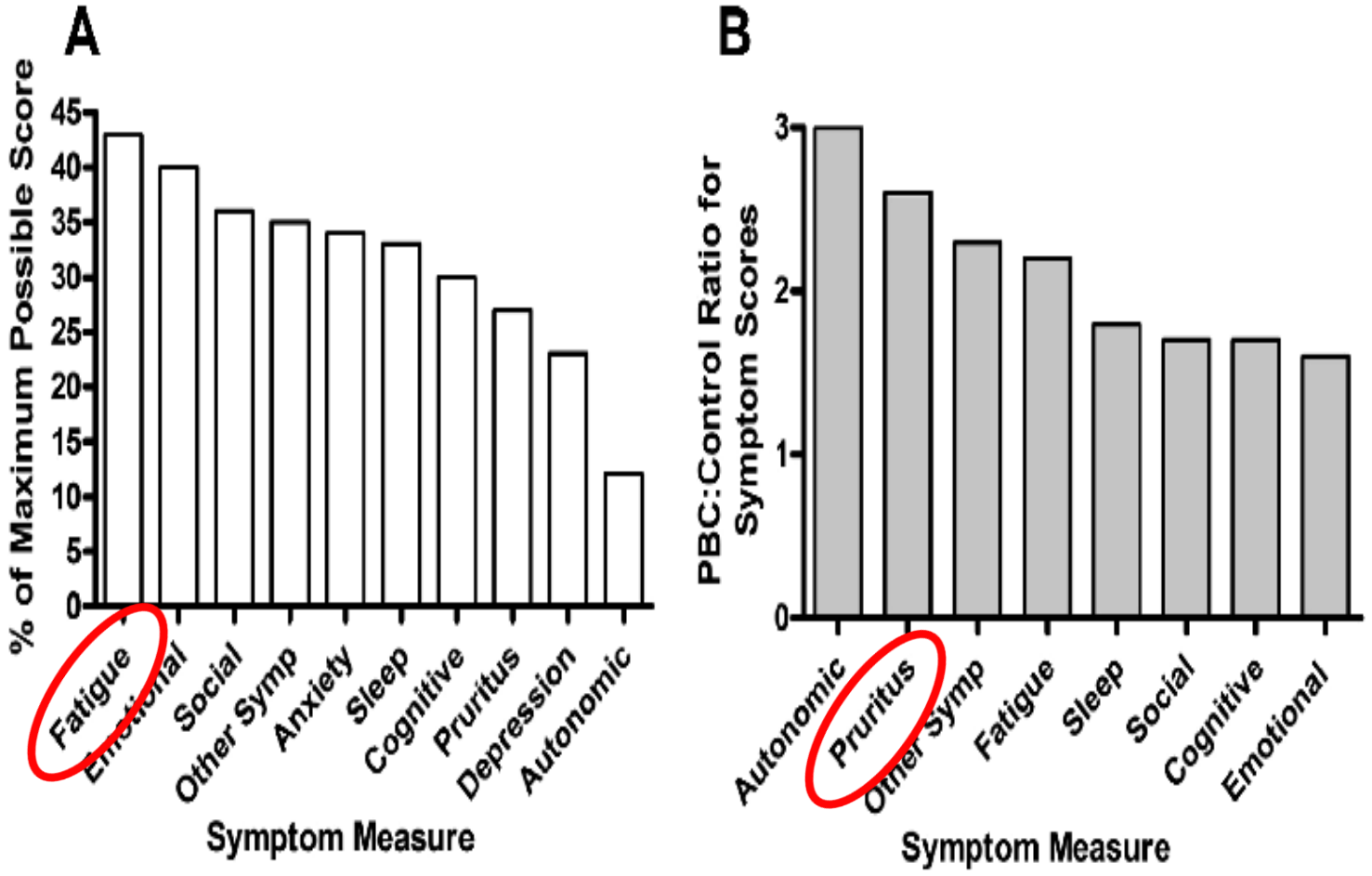
Carbone *et al* Gastroenterology 2013

I. Importance of pruritus in PBC

1. Itch is common in PBC and itch intensity is higher in younger patients.

2. Pruritus has negative impact on quality of life.

Impact of pruritus on QoL UK-PBC Cohort, n=2300



Mells *et al* Hepatology 2013

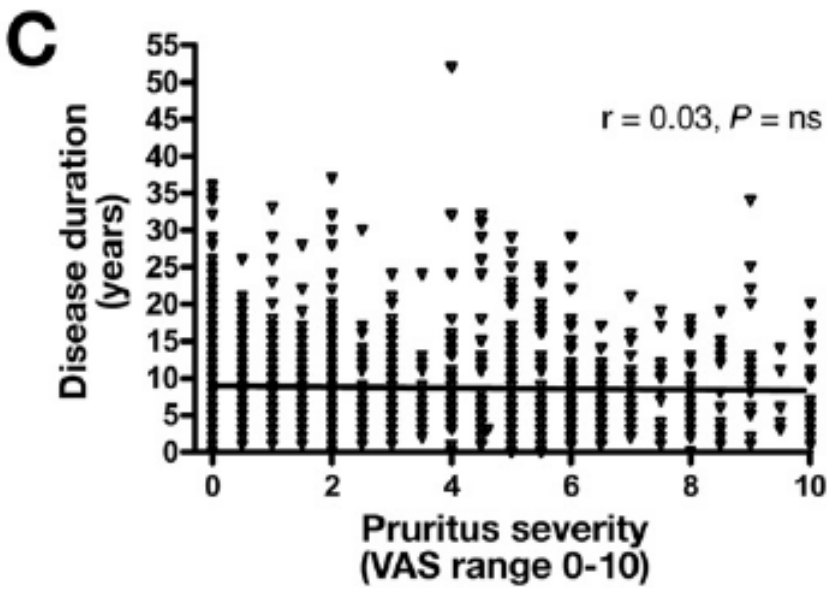
I. Importance of pruritus in PBC

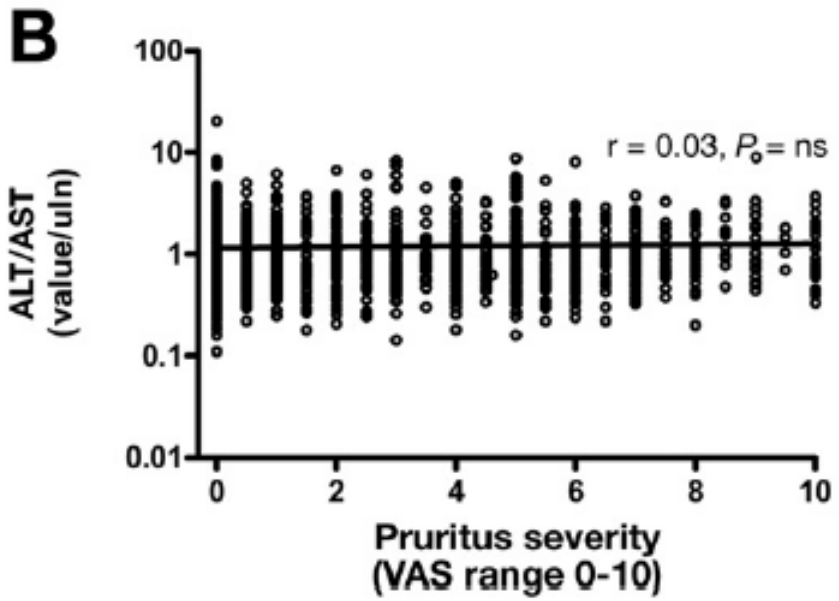
1. Itch is common in PBC and itch intensity is higher in younger patients.

2. Pruritus has negative impact on quality of life

3. Pruritus severity is independent of disease duration and LFTs

Itch severity has no association with disease duration or LFTs





Carbone *et al* Gastroenterology 2013

II. Current Management of Pruritus

Recommendation

26. EASL recommends the evaluation of all patients for the presence of symptoms, particularly pruritus, sicca complex and fatigue. Whilst end-stage liver disease is associated with progressive symptom burden, severity of symptoms does not necessarily correlate with stage of disease in PBC (**III**, **1**).

EASL Guidelines 2017

Rule out/ “test and treat”

- Biliary obstruction e.g. stones, strictures
- Iron deficiency anaemia
- Hypo/hyperthyroidism
- Diabetes mellitus
- Uraemia

Polat et al. Am J Clin Dermatol. 2008;9(1):39-44.

Table 2 Currently available drugs for the treatment of pruritus in PBC

Approach	Drug	Dose (/day)	Proposed mechanism of action
First line	Colestyramine Colesevelam	4–16 g 3.75 g in 2–3 divided doses	Bile acid resins. Bind to the bile acids, reduce their reabsorption in the intestine and increase faecal excretion
Second line	Rifampicin (rifampin)	150–600 mg	▶ Pregnane X receptor (PXR) agonist ▶ PXR-mediated down regulation of ATX transcription ▶ Inducer of microsomal enzymes leading to increased metabolism of endogenous pruritogenic compounds (including opiates) ▶ Inhibition of bile salt uptake by hepatocytes ▶ Altered intestinal metabolism of pruritogens by antibiotic effect on the intestinal microbiota
Third line	Naltrexone	50 mg	Mu opioid antagonist
Fourth line	Sertraline	100 mg	Serotonin reuptake inhibitor, antipruritic mechanism unclear

Hegade VS, Moreea S *et al*, Textbook of Geriatrics 2014
Hegade *et al*, Frontline Gastro 2015

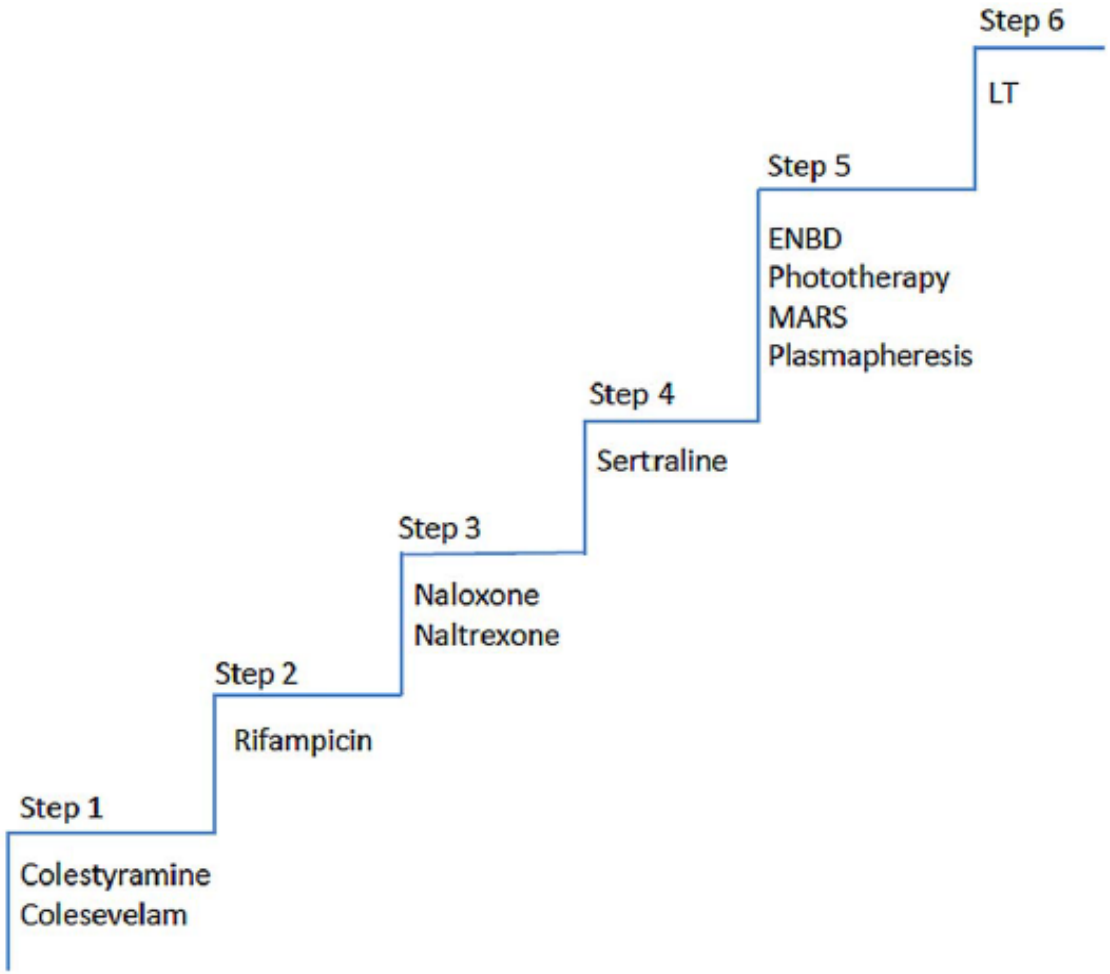
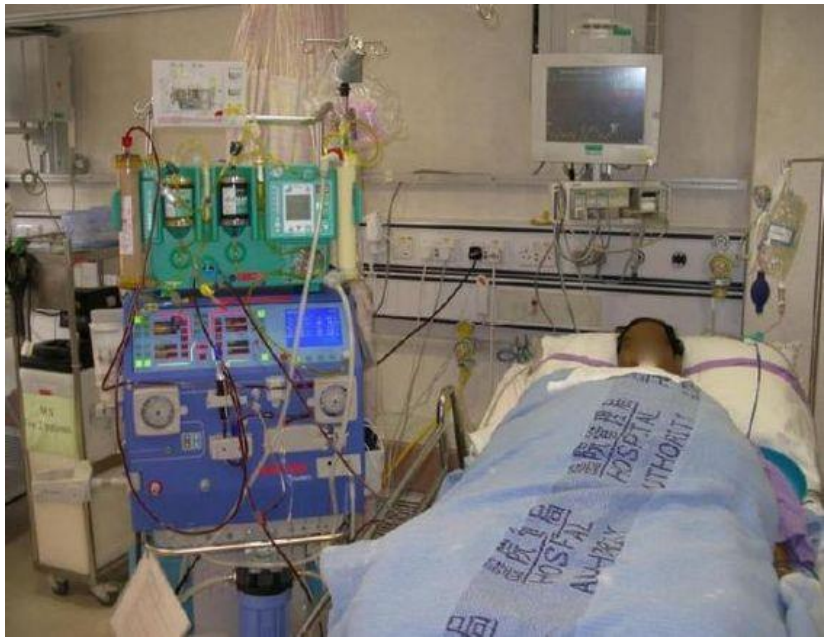


Figure 1 Cholestatic pruritus treatment ladder. If there is no response with one category of drugs, 'move up' the ladder. Patient may need combination of treatments to achieve and/or maintain symptom remission. Particular treatments may not be suitable for all patients. ENBD, endoscopic nasobiliary drainage; MARS, molecular adsorbent recirculating system; LT, liver transplantation.

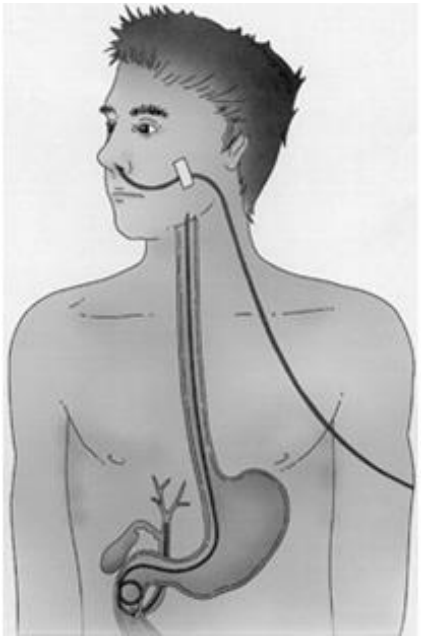
Hegade *et al* Frontline gastro 2015

Rescue treatments for severe pruritus

UV phototherapy



Albumin dialysis (MARS®)



Nasobiliary drainage

Courtesy: Google images

Nasobiliary drainage in Cholestatic Pruritus

AP&T Alimentary Pharmacology and Therapeutics

The safety and efficacy of nasobiliary drainage in the treatment of refractory cholestatic pruritus: a multicentre European study

V. S. Hegade*, M. Krawczyk[†,‡], A. E. Kremer[§], J. Kuczka[§], F. Gaouar[¶], E. M. M. Kuiper**, H. R. van Buuren**, F. Lammert[†], C. Corpechot[¶] & D. E. J. Jones*

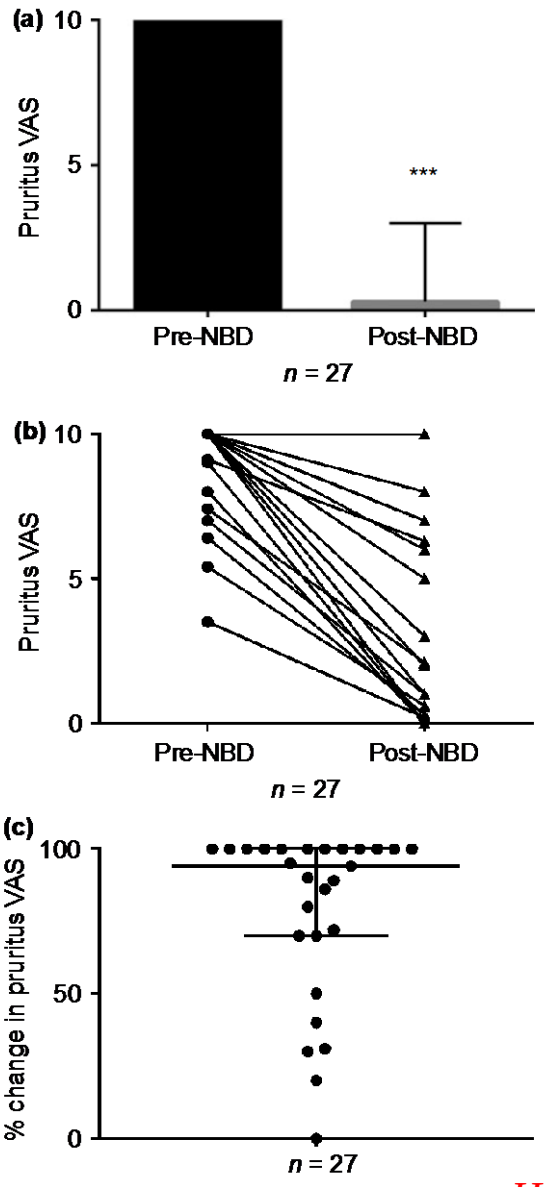
Hegade VS et al., AP&T 2015

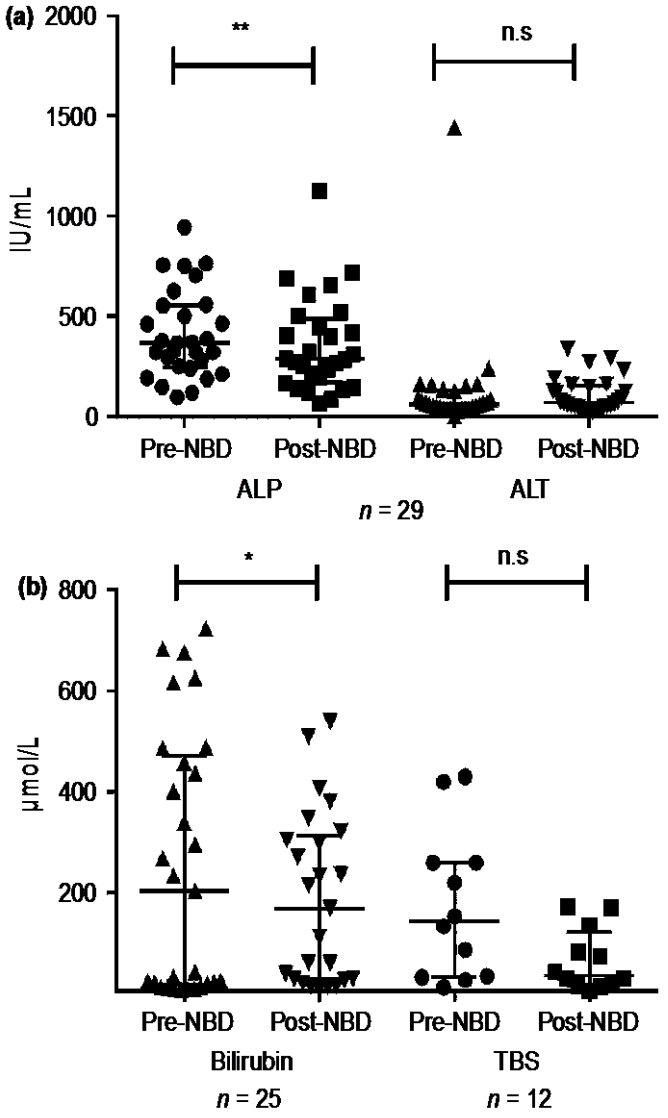
Patients treated with nasobiliary drainage (NBD) for cholestatic pruritus
(*n* = 27)
-Rotterdam, *n* = 7
-Paris, *n* = 6
-Newcastle, *n* = 5
-Erlangen, *n* = 5
-Homburg, *n* = 4

→ Excluded, *n* = 0

Included in the study
n = 29 cases
(two patients underwent NBD twice)

Cases with incomplete data
-Pruritus, *n* = 2
-Serum bilirubin, *n* = 4
-Total serum bile salts, *n* = 17





Hegade VS et al., AP&T 2015

Liver transplantation (LT)

- The only definitive cure !

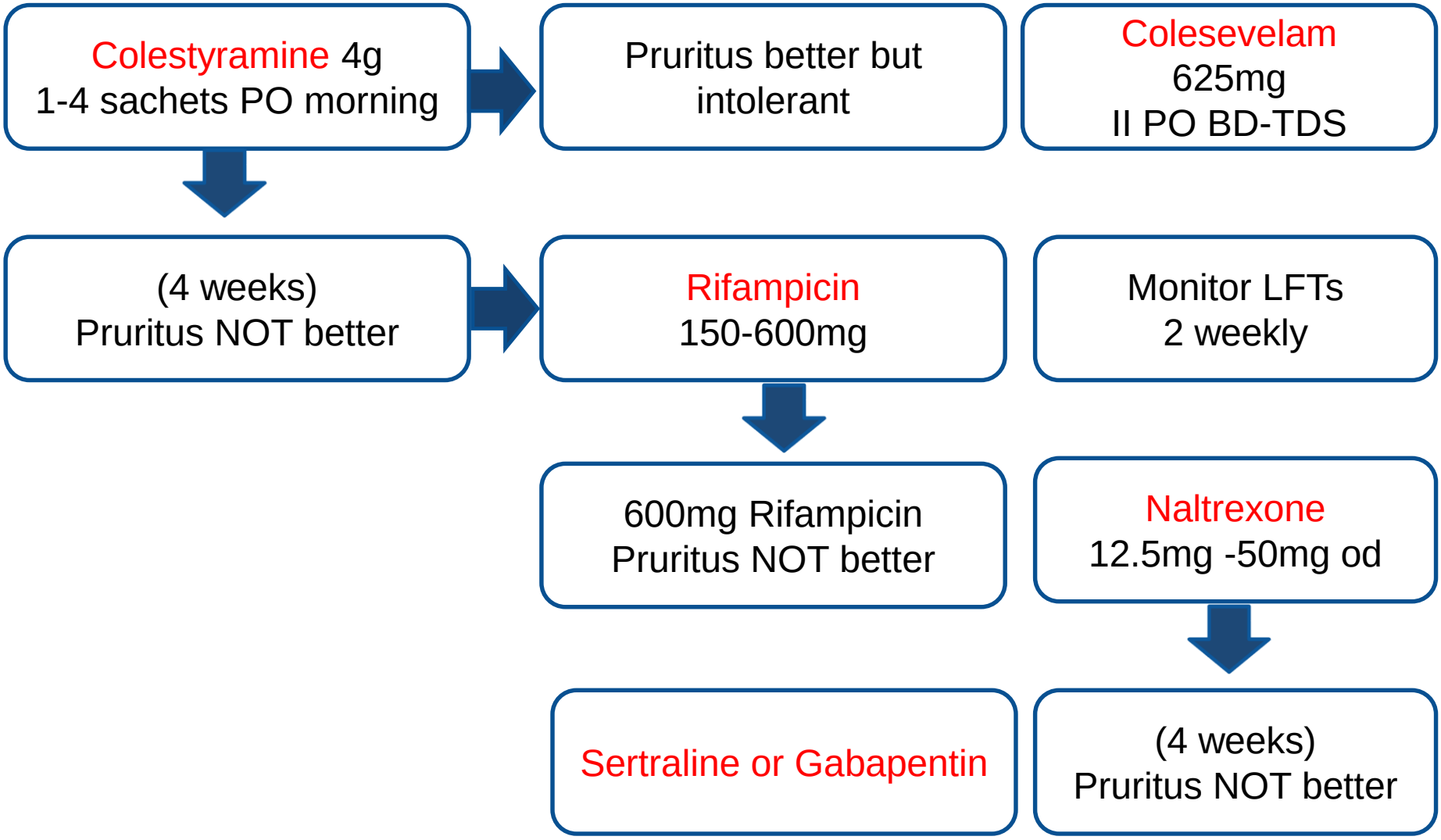
- Highly effective
- Rapid reduction in severity (within ~24hr of LT)

- *Refractory pruritus in PBC is an indication for LT*

How do I treat itch in liver disease?

Pruritus + Rash	Refer to Dermatology
US abd +/- MRCP	Rule out biliary obstruction
Check for other treatable causes of pruritus	• Hypothyroidism • Iron def. anaemia
Assess severity and extent of pruritus	Use VAS, NRS, PBC-40 itch domain
Mild or localised pruritus	Topical therapy only
Mod-severe or generalised pruritus	Topical + Systemic therapy

Systemic therapy: “4 week rule”



III. Challenges in managing pruritus in PBC

1. UDCA does not improve pruritus

Analysis 1.14. Comparison 1 UDCA versus placebo or no intervention, Outcome 14 Pruritus.

Review: Ursodeoxycholic acid for primary biliary cirrhosis

Comparison: 1 UDCA versus placebo or no intervention

Outcome: 14 Pruritus

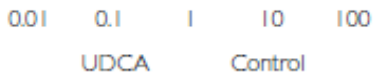
Study or subgroup	UDCA n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heathcote 1994	72/111	72/111		42.2 %	1.00 [0.82, 1.21]
Leuschner 1989	1/10	1/10		0.6 %	1.00 [0.07, 13.87]
Lindor 1994	53/71	47/58		30.3 %	0.92 [0.77, 1.11]
Oka 1990	5/26	5/26		2.9 %	1.00 [0.33, 3.05]
Poupon 1991	22/73	25/73		14.7 %	0.88 [0.55, 1.41]
Vuoristo 1995	15/30	16/31		9.2 %	0.97 [0.59, 1.59]
Total (95% CI)	**321**	**309**		**100.0 %**	**0.96 [0.84, 1.09]**

Total events: 168 (UDCA), 166 (Control)

Heterogeneity: $Chi^2 = 0.49$, $df = 5$ ($P = 0.99$); $I^2 = 0.0\%$

Test for overall effect: $Z = 0.67$ ($P = 0.51$)

Test for subgroup differences: Not applicable



- UDCA did not influence the number of patients with pruritus
  (168/321 (52.3%) vs. 166/309 (53.7%); RR 0.96 (95% CI 0.84-1.09)

Rudic *et al* Cochrane Syst Review 2012

Side effects of current drugs

- Cholestyramine/Questran:
  - unpleasant taste, bloating, diarrhoea/constipation

- Rifampicin:
  - liver injury (hepatitis), liver failure, haemolysis

- Naltrexone:
  - Opioid withdrawal like reaction (abdominal pain, tachycardia, high BP, goose bumps, nightmares)

Challenges in managing pruritus

1. UDCA does not improve pruritus
2. Current drug treatments have side effects
3. Obeticholic acid (OCA), makes pruritus worse !

OCA makes pruritus worse

Table 2. Incidence of Adverse Events of 10% or More in any Treatment Group.*

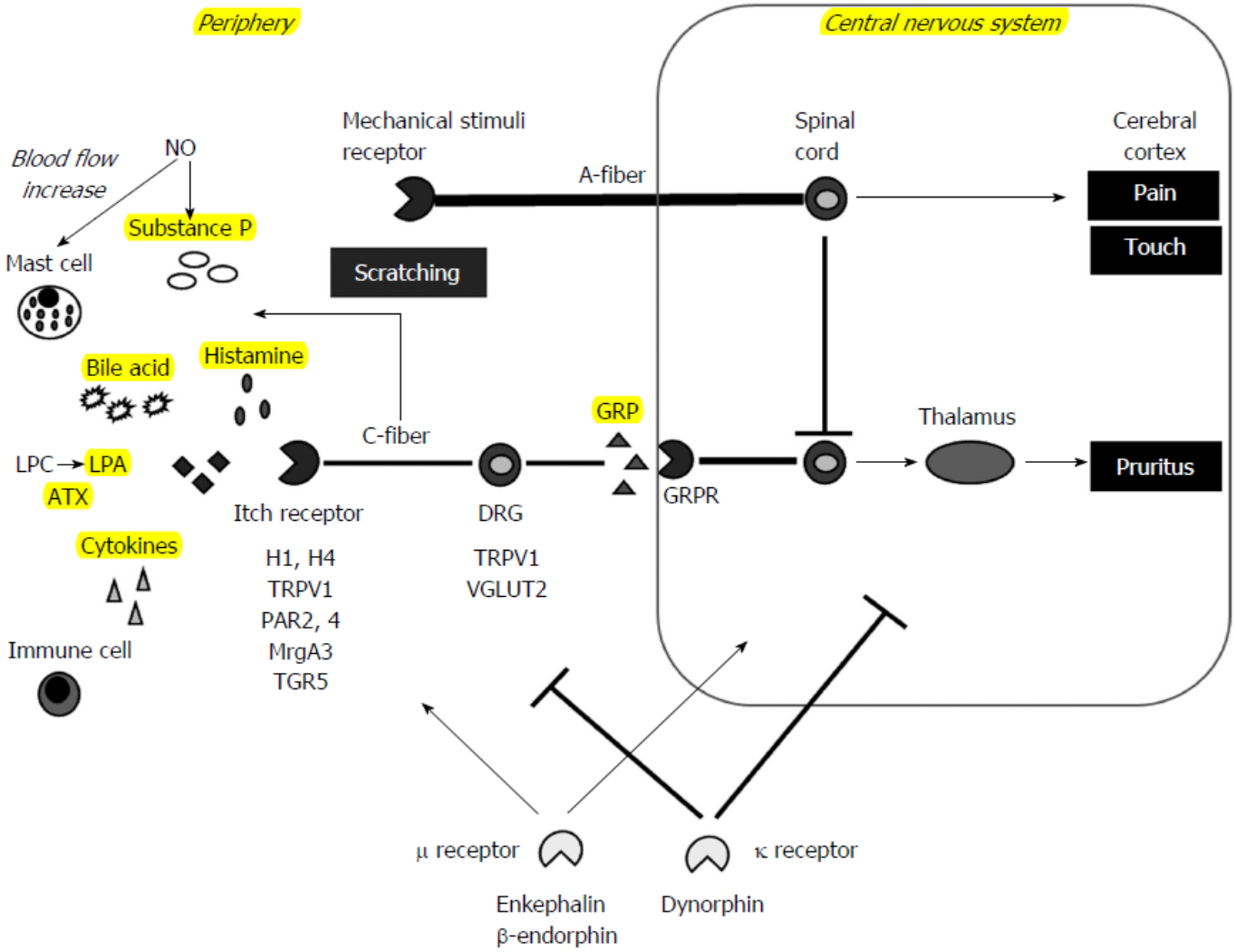
Event	Double-Blind Phase			Open-Label Extension
	Placebo (N = 73)	Obeticholic Acid, 5–10 mg (N = 70)	Obeticholic Acid, 10 mg (N = 73)	Total Obeticholic Acid (N = 193)
	number of patients (percent)			
Pruritus	28 (38)	39 (56)	50 (68)	138 (72)

Nevens et al NEJM 2016

Challenges in managing pruritus

1. UDCA does not improve pruritus
2. Current drug treatments have side effects
3. Obeticholic acid (OCA), makes pruritus worse
4. Pathophysiology is unclear

Mechanism of pruritus



Tajiri K et al WJG 2017

IV. Future directions

New evidence for Bile Acids causing Itch

The TGR5 receptor mediates bile acid–induced itch and analgesia

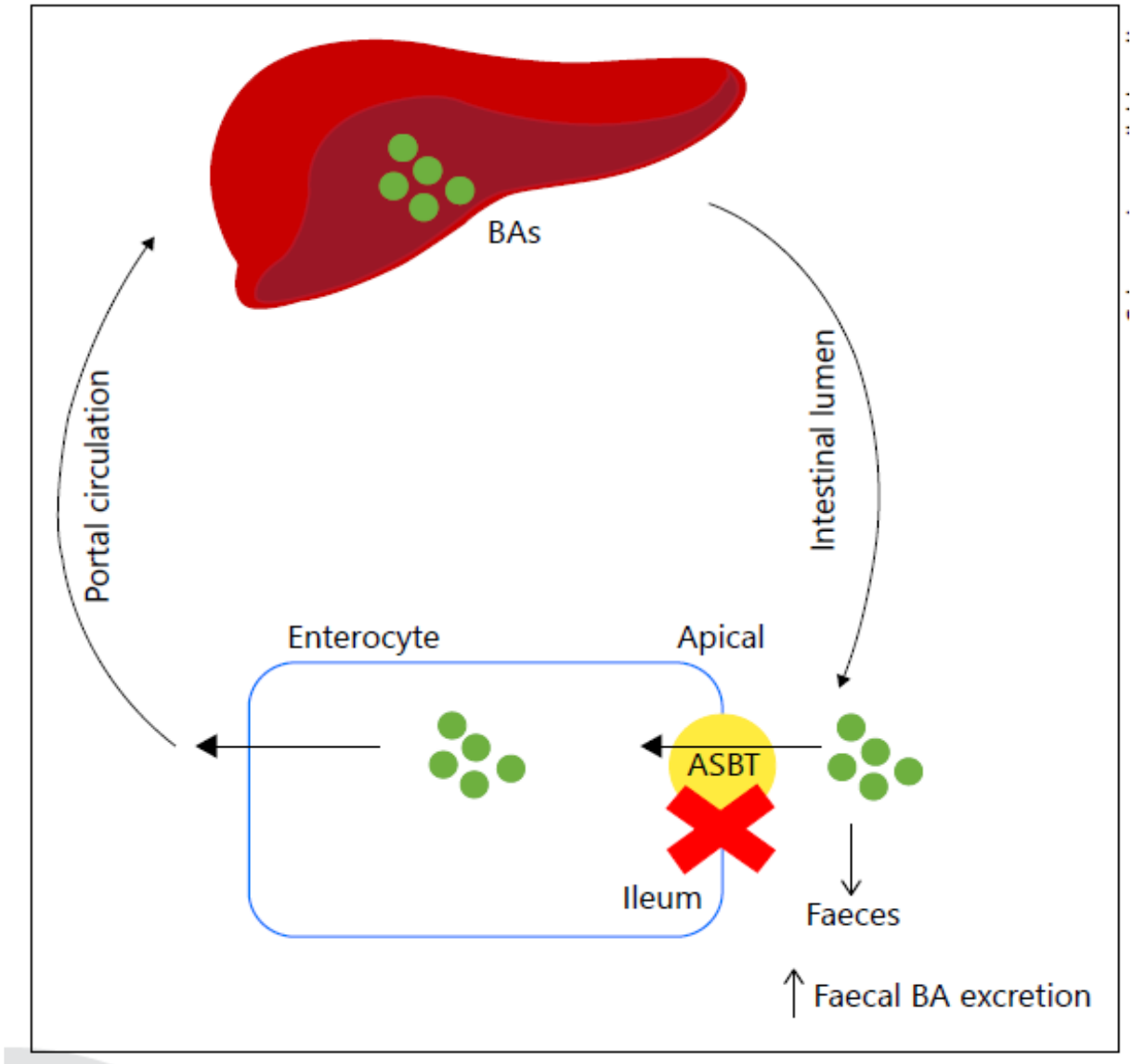
Farzad Alemi,[1] Edwin Kwon,[1] Daniel P. Poole,[2] TinaMarie Lieu,[3] Victoria Lyo,[1] Fiore Cattaruzza,[1] Ferda Cevikbas,[4] Martin Steinhoff,[4] Romina Nassini,[5] Serena Materazzi,[5] Raquel Guerrero-Alba,[6] Eduardo Valdez-Morales,[6] Graeme S. Cottrell,[7] Kristina Schoonjans,[8] Pierangelo Geppetti,[5] Stephen J. Vanner,[6] Nigel W. Bunnett,[3] and Carlos U. Corvera[1]

Gastroenterology 2014;147:1417–1428

The Bile Acid Receptor TGR5 Activates the TRPA1 Channel to Induce Itch in Mice

TinaMarie Lieu,[1] Gihan Jayaweera,[1] Peishen Zhao,[1] Daniel P. Poole,[1,2] Dane Jensen,[1] Megan Grace,[3] Peter McIntyre,[3] Romke Bron,[2] Yvette M. Wilson,[2] Matteus Krappitz,[4] Silke Haerteis,[4] Christoph Korbmacher,[4] Martin S. Steinhoff,[5] Romina Nassini,[6] Serena Materazzi,[6] Pierangelo Geppetti,[6] Carlos U. Corvera,[7] and Nigel W. Bunnett[1,8]

Ileal Bile Acid Transporter (IBAT or ASBT)



Hegade et al, *Ther Adv Gastr* 2016

IBAT Inhibitor as new drug treatment for itch in PBC

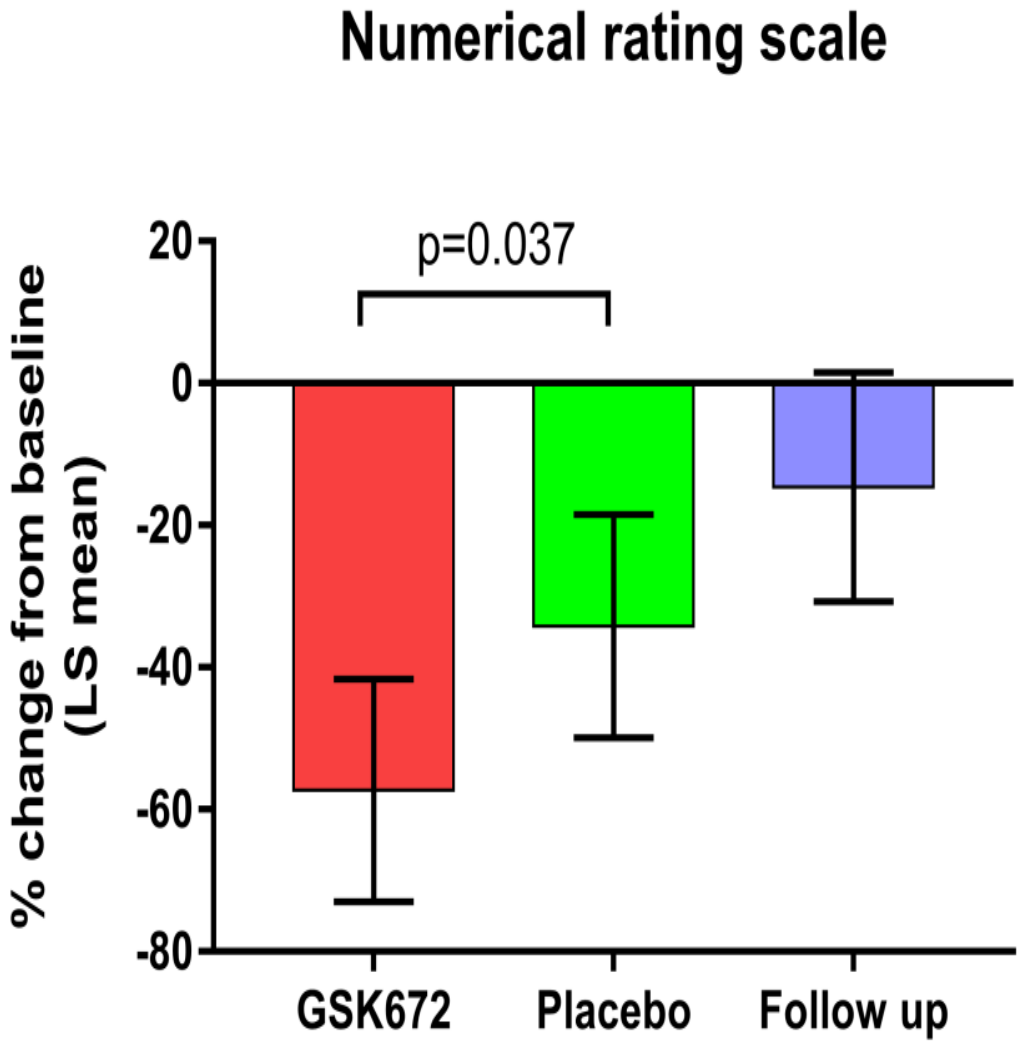
Does IBAT inhibitor drug reduce itch in patients with PBC?

Effect of ileal bile acid transporter inhibitor GSK2330672 on pruritus in primary biliary cholangitis: a double-blind, randomised, placebo-controlled, crossover, phase 2a study

Vinod S Hegade, Stuart F W Kendrick*, Robert L Dobbins, Sam R Miller, Douglas Thompson, Duncan Richards, James Storey, George E Dukes, Margaret Corrigan, Ronald P J Oude Elferink, Ulrich Beuers, Gideon M Hirschfield, David E Jones*

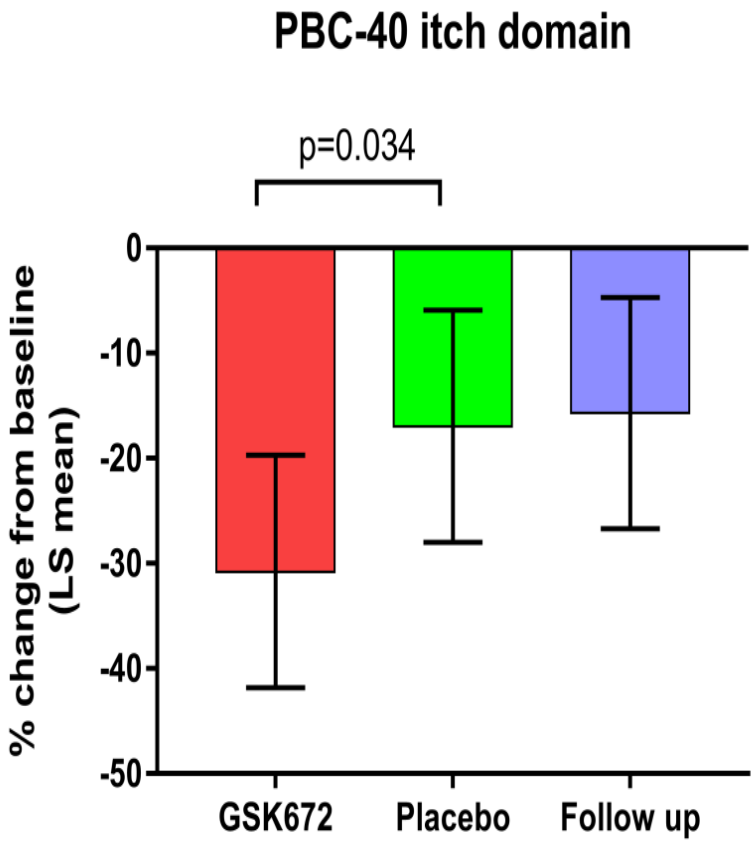
Lancet 2017; 389: 1114–23

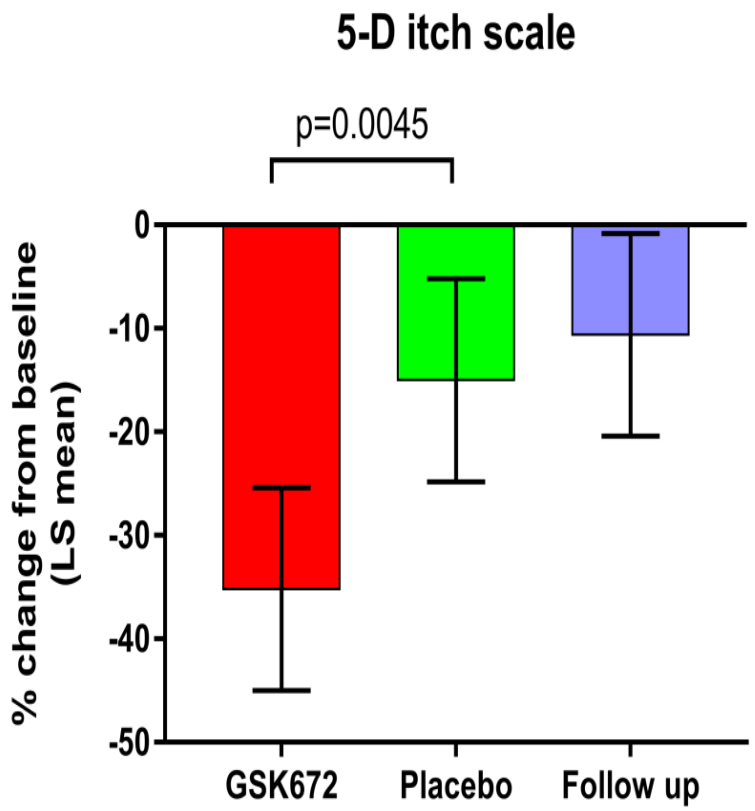
NRS Itch Intensity: % change from baseline



Hegade et al, *Lancet*, 2017

PBC-40 and 5-D itch: % change from baseline





Hegade et al, *Lancet*, 2017

	Placebo run-in (n=22), n (%)	GSK2330672 (n=21), n (%)	Placebo (n=21), n (%)
Participants with any adverse event	15 (68)	17 (81)	17 (81)
Gastrointestinal system			
Diarrhoea	1 (5)	7 (33)	1 (5)
Upper abdominal pain	0	3 (14)	1 (5)
Abdominal distension	0	3 (14)	1 (5)
Abdominal pain	0	3 (14)	0
Vomiting	0	1 (5)	2 (10)
Nausea	0	2 (10)	0
Nervous system			
Headache	7 (32)	6 (29)	7 (33)
Dizziness	1 (5)	1 (5)	2 (10)
Paraesthesia	0	0	2 (10)
Infections			
Nasopharyngitis	0	1 (5)	2 (10)
General			
Fatigue	0	0	2 (10)

Adverse events were monitored from day 1 to 56 of the study including follow-up period. Data are in n (%). The listed adverse events (any severity) have an incidence greater than one patient (5%) in any treatment period.

Table 2: Summary of adverse events

Hegade et al, *Lancet*, 2017

Itch in PBC: GLIMMER of hope ?

gsk do more feel better live longer

The GLIMMER, is our newsletter for all GSK and investigator site staff associated with GLIMMER - *GSK2330672 triaL of Ibat inhibition with Multidose Measurement for Evaluation of Response* – a dose-response study of the ileal bile acid transporter (IBAT) inhibitor GSK2330672 in people with moderate to severe pruritus (itching) associated with primary biliary cholangitis (PBC).

Recruitment and Update

Thank you for your continued efforts on this study !

- ◊ 22 subjects need to be randomized to complete recruitment for the GLIMMER study
- ◊ 5 Months until LSFV milestone on 10September 2019

- 10 countries initiated
- 74 sites initiated
- 205 subjects screened
- 43 screen failures
- 162 subjects completing V2
- 35 baseline failures
- 118 subjects randomized
- 95 subjects completed the study
- 09 subjects withdrawn from study
- 09 subjects between V2-V3

We have a name .....Linerixibat

Final Conclusions (1)

- PBC is the most common cholestatic liver disease
- All PBC patients should be treated with UDCA
- Assess response to UDCA at 12 months post treatment
- UDCA non-responders → second line treatment
- Obeticholic acid and Bezafibrate

Final Conclusions (2)

- UDCA and current anti-pruritic treatments do not fully meet patient expectations
- OCA is unlikely to be useful in patients with pruritus
- Newer drugs (?Bezafibrate) are needed for symptom control
- IBAT inhibitors have the potential to reduce pruritus and may have beneficial effects on cholestasis
- GSK2330672 (Linerixibat) is promising but needs more evaluation

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gsk

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Liver NORTH LIVER PATIENT SUPPORT